Compliments of
Missouri Heart Association—811 Cherry, Columbia, Missouri

Modern Concepts of Cardiovascular Disease

Published monthly by the AMERICAN HEART ASSOCIATION
44 EAST 23RD STREET, NEW YORK 10, NEW YORK

Editor
HOWARD P. LEWIS, M.D.
Portland, Oregon

Associate Editor
HERBERT E. GRISWOLD, JR., M.D.
Portland, Oregon

Associate Editor
FRANKLIN J. UNDERWOOD, M.D.
Portland, Oregon

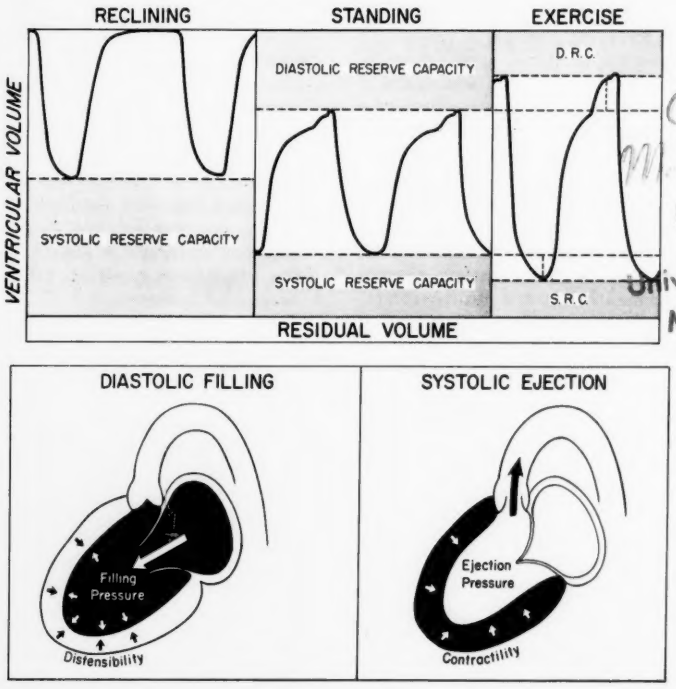
Copyright 1958 by the American Heart Association

Vol. XXVII **AUGUST, 1958** **No. 8**

WORK OF THE HEART*

The useful work performed by the heart during each cardiac cycle is the sum of potential energy (volume ejected times change in pressure) plus the kinetic energy of the outflowing blood. According to traditional concepts, the amount of energy released by the contracting myocardium is determined by the diastolic length of the myocardial fibers (Starling's Law of the Heart). On this basis, the diastolic volume of the heart should be small and the systolic ejection quite complete when the load on the heart is minimal. An increase in the amount of energy released by the heart should be accompanied by distention of the ventricles during diastole. This concept has been amply confirmed in isolated hearts or heart-lung preparations, but experi-

* From the Department of Physiology and Biophysics, University of Washington School of Medicine, Seattle, Washington. This investigation was supported (in part) by a research grant from the National Heart Institute of the National Institutes of Health, Public Health Service, and the American Heart Association.

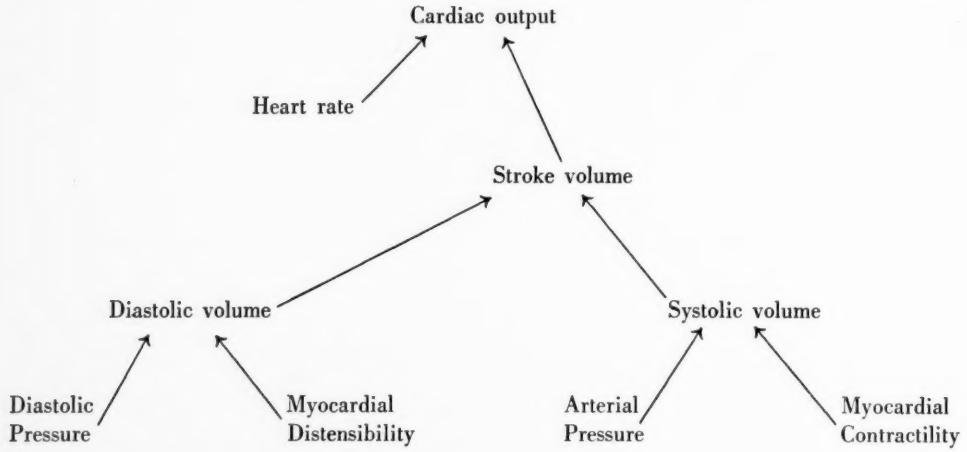


Clendening Medical Library
OCT 25 1961
University of Medical Center

Figure 1. **In the normal** resting dog or human, the ventricles are distended to their maximal volume during each diastolic filling. The systolic reserve capacity is also maximal. The ventricular volume diminishes on standing so that stroke volume can be increased by either greater diastolic filling, greater systolic ejection, or both. The diastolic filling is determined by the relationship between filling pressure and "distensibility"; systolic ejection by the outflow and the "contractility."

Table I

Factors Affecting Cardiac Output



ments on intact animals[1, 2] and human subjects[3-6] have demonstrated that the heart normally functions at large systolic and diastolic volumes. In fact, the diastolic volume of the heart is maximal when a subject is at rest in a horizontal position.[7, 8] Any change in status or position results in a diminution in both the systolic and the diastolic dimensions of the heart. Thus, the ventricles of standing dogs or humans function between the maximum diastolic and the minimum systolic sizes (Figure 1). The extent to which the ventricles can distend during filling can be regarded as a *diastolic reserve capacity* and the additional blood which can be ejected during contraction serves as a *systolic reserve capacity*. The normal heart can utilize either, or both, of these reserve capacities during cardiovascular adjustments requiring increased stroke volume.

Factors Influencing Stroke Volume

The stroke volume represents the difference between the diastolic volume and the systolic volume (Table I). The diastolic volume is determined by the effective filling pressure, which tends to distend the ventricular myocardium, and the resistance afforded by the ventricular wall to stretch ("distensibility"). Many mechanisms which can alter the ventricular filling pressure are easily visualized, but the factors which influence the "distensibility" of the ventricles are not well understood. Physiological experiments have demonstrated that greater diastolic distention without a corresponding increase in filling pressure may follow administration of epinephrine. Such a change in "distensibility" corresponds to a variation in "tone" of the myocardium similar to that in visceral smooth muscle. Thus, the diastolic distention of the ventricles must be considered in terms of both filling pressure and "distensibility," since the resting tension of myocardium can be altered by autonomic hormones or discharges along autonomic nerves (Figure 1).

Factors causing the ventricles to empty more completely at one time than another must also be considered. As the ventricles contract, blood is ejected from the chamber into the corresponding artery only so long as the ventricular myocardium maintains a ventricular pressure higher than the corresponding arterial pressure. The tension of contracting myocardial fibers tends to diminish as they shorten. Thus, ventricular ejection will cease when the myocardial fibers cannot continue to shorten without permitting the ventricular pressure to fall below the arterial pressure. The degree of systolic emptying of the ventricles is influenced by many factors, including the systemic arterial pressure, the heart rate, and the myocardial "contractility."

The term "contractility" is widely used but rarely defined. It generally refers to the effects of administering epinephrine or of stimulating sympathetic nerves to the heart. Increased "contractility" implies that the contracting myocardium develops greater tension more rapidly at the onset of systole, the duration of systole is shortened, the ventricular pressures drop more rapidly at the end of systole, systolic pressure is higher, and systolic ejection is more complete. A growing mass of evidence indicates that the traditional concepts, based on Starling's Law

of the Heart, do not explain adequately the cardiac responses observed in intact animals and man. The effects of changes in heart rate and "contractility" are so prominent in intact animals that the role of Starling's law is largely obscured. The most effective mechanism for increasing myocardial contractility under normal conditions is through increased activity along sympathetic nerves to the heart. Neural control mechanisms now appear to be the primary and prepotent mechanism of cardiac control.

Acute Ventricular Failure

In the past, heart failure has frequently been attributed to a progressive dilation of the heart beyond the normal functional range in which Starling's Law of the Heart operates. On this basis, heart failure has been viewed as an overextension of a normal cardiac response to a load. The fact that the ventricles normally become smaller rather than larger during exercise indicates that this view should be reconsidered. The progressive distention of a failing ventricle means that a larger residual volume of blood remains in the ventricles at the end of systole. The reduced degree of systolic emptying suggests that the *systolic reserve capacity* cannot be utilized. In other words, the "contractility" of the ventricular myocardium is deficient, and the *diastolic reserve capacity* is utilized to its maximum extent. Under these conditions, the stroke volume should be about as great at rest as that which can be attained during exertion. Such inability to increase stroke volume has been directly demonstrated in patients with heart failure. The concept that heart failure results from a severe reduction in myocardial contractility is more a description than an explanation, but may suggest rational approaches to research and to patient care.

CARDIAC RESPONSES TO CHRONIC LOADS

Knowledge concerning the functional characteristics of myocardium and the architecture of the ventricular chambers makes it possible to predict the manner in which the right or the left ventricle will respond to the common types of loads resulting from various disease processes. The nature of the load carried by the right and left ventricles is determined in part by the characteristics of the circulatory bed which they serve. The architecture of the ventricular chambers reflects the kind of load they bear.[9, 10] For example, the left ventricle is a roughly cylindrical cavity enclosed within thick myocardial walls, the ventricular septum being considered a portion of the left ventricle (Figure 2*A*). A power-

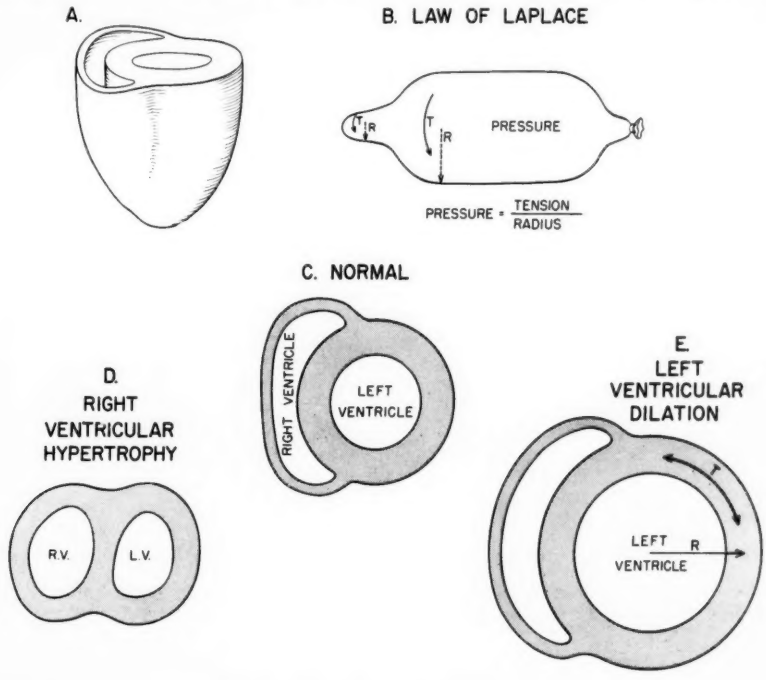


Figure 2. (*A*) The anatomical distinction between the thick-walled left ventricle and the thin right ventricular wall is indicated schematically. (*B*) The Law of Laplace states that if the internal pressure is constant, the tension in the wall increases with the radius of the hollow viscus. The relationships between wall thickness and cavity volume are indicated schematically for: (*C*) the normal heart, (*D*) right ventricular hypertrophy and (*E*) left ventricular dilation.

ful cuff of myocardium encircles the chamber like a clenched fist. The surface area of the left ventricle is small in relation to the contained volume so that the thick walls function as a high-pressure pumping system. In contrast, the right ventricular chamber is a narrow space between two broad surfaces, being merely a cleft between the ventricular septum and the thin free wall. In short, the right ventricle has a very large surface area per unit of contained volume, and serves as an effective volume pump against a low outflow resistance. Like a bellows, the right ventricle ejects large volumes with relatively slight degrees of myocardial shortening. Right ventricular outputs three times the normal resting level are frequently sustained for years in some patients with large atrial septal defects and little pulmonary hypertension. On the other hand, the normal right ventricle may fail rapidly when suddenly forced to pump blood against a high outflow pressure (*e.g.*, acute pulmonary hypertension from pulmonary embolism). The difference between the architecture of the right and left ventricles can be interpreted in terms of the tension which must be developed by the contracting myocardium according to the Law of Laplace.

The Law of Laplace

The pressure *(P)* in a hollow viscus is determined by the relationship between the tension *(T)* and the radius *(r)* of its walls in accordance with the formula:

$$P = \frac{T}{r},$$

the Law of Laplace. This principle is easily demonstrated by means of a partially inflated balloon (Figure 2*B*). Although the internal pressure is equal throughout the balloon, the wall is much more tense in the region where the radius is greater.[11] The undistended portion can be easily compressed between the fingers while the expanded wall resists indentation. The Laplace relationship also helps to explain how thin-walled vascular capillaries can support high pressures.[12] For example, the thick-walled aorta supports a mean pressure of about 100 mm. Hg. Capillaries 1 M. below the heart also support a pressure of about 100 mm. Hg with little more than a single layer of epithelial cells. Because of the tremendous difference in radius, the wall tension of the aorta is more than 2000 times greater than that of the capillary. This same principle influences the amount of tension which must be developed by myocardial fibers to elevate ventricular pressure.

Right Ventricular Responses to Volume and Pressure Loads

The free wall of the right ventricle approximates a segment of a sphere with a relatively large radius. For this reason, the right ventricular chamber can accommodate relatively large increments of volume with a very slight distention or lengthening of myocardial fibers. Similarly, relatively large volumes of blood can be ejected by slight degrees of myocardial shortening. For this reason, the right ventricle can readily accommodate a greatly increased stroke volume over long periods of time with little visible distention of the chamber and relatively slight increase in the degree of myocardial shortening. As mentioned above, the right ventricle rapidly fails when suddenly confronted with greatly increased outflow pressure, as occurs with pulmonary embolism. In order to elevate right ventricular pressure to high levels, the myocardial fibers would be forced to develop tension beyond their capability, as predicted from the Law of Laplace. In other words, the right ventricle is effective as a volume pump, and suffers a mechanical disadvantage when acting against high outflow pressures. If pulmonary hypertension is present at birth or develops gradually, the right ventricle develops a thick wall and a conformation which resemble those of the normal left ventricle (Figure 2*D*). In short, the right ventricle is converted into a high-pressure pumping chamber when confronted with a chronic pressure load.

Left Ventricular Responses to Volume and Pressure Loads

When the left ventricle is confronted by a sustained pressure load (*e.g.*, aortic stenosis or essential hypertension) the walls become thicker through hypertrophy of the individual myocardial fibers. Individual myocardial fibers may grow from a normal diameter of about 16 μ to a diameter of 32 μ. Apparently, further thickening of the fibers so increases the distance of diffusion to the center of the fiber that oxygen delivery and removal of wastes become impeded.[13] The hypertrophied fibers apparently can exert increased contractile tension. Left ventricular dilation is not an appropriate response to increased intraventricular pressure because the myocardial fibers in a distended chamber must exert even more tension than those in a small chamber. Thus, in accordance with the Law of Laplace, the left ventricle typically remains relatively small in the face of essential hypertension or aortic stenosis. Dilation may indicate the appearance of relative myocardial ischemia.

When the left ventricle must pump large stroke volumes, either the myocardial fibers must shorten more or the ventricular chamber must dilate. The myocardium in a dog's heart shortens about 3 to 5 per cent during normal systole.[14] The myocardium functions most effectively when its relative shortening remains small, so the typical response to a sustained volume load is dila-

tion. When the ventricle becomes distended, the myocardial tension must increase to maintain the same systolic blood pressure:

$$\left(P = \frac{T}{r}\right)$$

so the myocardial fibers become hypertrophied. For this reason, chronic left ventricular dilation is almost always accompanied by some myocardial hypertrophy. Chronic volume loads are also imposed when a sustained increase in ventricular ejection is required by such conditions as insufficiency of aortic or mitral valves, arteriovenous fistulae, Paget's disease, and hyperthyroidism. The largest hearts result from massive left ventricular dilation in patients with severe aortic regurgitation. In such cases, the walls are thin in relation to the chamber size, and the surface area is greatly increased. In this sense, the distended left ventricle resembles the normal right ventricle. The right and left ventricular adaptations to chronic pressure and volume loads have been oversimplified in this discussion. More detailed analysis of the changes in ventricular architecture has been reported by Grant.[15]

ROBERT F. RUSHMER, M.D.
Professor of Physiology
Department of Physiology and Biophysics
University of Washington School of Medicine
Seattle, Washington

REFERENCES

1. Rushmer, R. F.: Heart size and stroke volume. Minnesota Med. **37**: 19, 1954.
2. Holt, J. P.: Regulation of the degree of emptying of the left ventricle by the force of ventricular contraction. Circulation Res. **5**: 281, 1957.
3. Liljestrand, G. Lysholm, E. and Nylin, G.: Immediate effects of muscular work on the stroke and heart volume in man. Skand. Arch. Physiol. **80**: 265, 1938.
4. Nylin, G.: On the amount of, and changes in, the residual blood of the heart. Am. Heart J. **25**: 598, 1943.
5. Bing, R. J., Heimbecker, R., and Falholt, W.: An estimation of the residual volume of blood in the right ventricle of normal and diseased human heart *in vivo*. Am. Heart J. **42**: 483, 1951.
6. Kjellberg, S. R., Lönroth, H., Rudhe, U., and Sjöstrand, T.: Relationship between heart volume and blood volume and its physiological and pathological variability. Acta med. Scandinav. **140**: 446, 1951.
7. Sjöstrand, T.: Volume and distribution of blood and their significance in regulating circulation. Physiol. Rev. **33**: 202, 1953.
8. Rushmer, R. F.: Residual volume of blood in the right and left ventricle. In World Trends in Cardiology: Part III, Blood Volume and Contractile Protein in Heart Muscle, pp. 96-103. Cain, A. S., Jr., ed. New York, Hoeber-Harper, 1956.
9. Rushmer, R. F.: Cardiac Diagnosis: A Physiologic Approach. Philadelphia, W. B. Saunders, 1955.
10. Rushmer, R. F., Crystal, D. K., and Wagner, C.: Functional anatomy of ventricular contraction. Circulation Res. **1**: 162, 1953.
11. Wolf, A. V.: Demonstration concerning pressure-tension relations in various organs. Science **115**: 243, 1952.
12. Burton, A. C.: On physical equilibrium of small blood vessels. Am. J. Physiol. **164**: 319, 1951.
13. Harrison, T. R.: Failure of the Circulation, ed. 2. Baltimore, Williams and Wilkins Company, 1939.
14. Rushmer, R. F.: Length-circumference relations of the left ventricle. Circulation Res. **3**: 639, 1955.
15. Grant, Robert P.: Architectonics of the heart. Am. Heart. J. **46**: 405, 1953.

A SPECIAL SCIENTIFIC PROGRAM

marking the opening of its new

CARDIOVASCULAR RESEARCH INSTITUTE

will be presented in the auditorium of the University of California Medical Center, San Francisco, on Thursday afternoon, October 23, 1958, from 2:00 to 5:00 P.M. Those attending the 31st Scientific Sessions of the American Heart Association are invited. The speakers will be:

Sir George Pickering, *Regius Professor of Medicine, University of Oxford, England*

Dr. I. Lyon Chaikoff, *Professor of Physiology, University of California, Berkeley*

Dr. Malcolm McIlroy, *First Assistant, Institute of Cardiology, London, England*

Dr. Julius H. Comroe, Jr., *Director, Cardiovascular Research Institute, University of California Medical Center, San Francisco*

Plan to arrive in San Francisco in time to attend this meeting! Seating capacity limited to 500. For tickets, apply to the Cardiovascular Research Institute, University of California Medical Center, San Francisco 22, California.

THE AMERICAN HEART ASSOCIATION

and

THE AMERICAN SOCIETY FOR THE STUDY OF ARTERIOSCLEROSIS

cordially invite you to attend their

JOINT SESSIONS

Genetic Factors in Cardiovascular Disease—A Symposium

Friday Morning, October 24, 1958 — 9:00 A.M. to 12:30 P.M.

Chairmen: Dr. Victor A. McKusick, *Baltimore, Maryland*
Dr. David Adlersberg, *New York, New York*

Hypertension	— Sir George Pickering, *Oxford, England*
	— Dr. Douglas R. Drury, *Los Angeles, California*
	— Dr. Caroline B. Thomas, *Baltimore, Maryland*
Atherosclerosis	— Dr. Frederick H. Epstein, *Ann Arbor, Michigan*
	— Dr. Richard H. Osborne, *New York, New York*
	— Dr. Arthur G. Steinberg, *Cleveland, Ohio*
Rheumatic Fever	— Dr. Paul A. Lembcke, *Los Angeles, California*
	— Dr. May G. Wilson, *New York, New York*
Congenital Malformations	— Dr. Victor A. McKusick, *Baltimore, Maryland*
	— Dr. Catherine A. Neill, *Baltimore, Maryland*

Discussion: Opened by Dr. Antonio Ciocco, *Pittsburgh, Pennsylvania*

Panels on Arteriosclerosis

Saturday Afternoon, October 25, 1958 — 2:00 to 5:00 P.M.

Emotional Factors in Atherosclerosis	— Dr. Louis N. Katz, *Chicago, Illinois,* Moderator
Association of Hypertension and Atherosclerosis	— Dr. A. C. Corcoran, *Cleveland, Ohio,* Moderator

(A list of speakers for the Saturday afternoon session is not yet available)

Civic Auditorium

San Francisco, California